23. The composition of ~~Claim~~ 22, wherein said chicken antibodies are derived from ~~chicken~~ eggs.

REMARKS

Claims 1-18 were pending and stand rejected. Applicant acknowledges the Examiner's withdrawal of the §§ 101 and 112 rejections entered in the July 2, 1999 Office Action. In the Office Action dated December 22, 1999, the Examiner made a number of arguments and rejections. For clarity, the rejections at issue are set forth by number in the order they are herein addressed:

(1) Claims 1-3 and 7-15 stand rejected under 35 U.S.C. § 103 as allegedly obvious over the combination of Starnes *et al.* (J. of Immun. Vol. 145, No. 12 [1990]; hereinafter "Starnes *et al.*") and Doherty *et al.* (J. of Immun. Vol. 149, No. 5 [1992]; hereinafter "Doherty *et al.*"); and

(2) Claims 1, 3-6 and 16-18 stand rejected under 35 U.S.C. § 103 as allegedly obvious over the combination of Starnes *et al.* and Doherty *et al.* in view of Emery *et al.* (U.S. Pat. No. 5,420,253; hereinafter "Emery *et al.*").

Applicant believes the present remarks traverse the Examiner's rejections. These remarks are presented in the same order as the above rejections.

1. The Examiner Improperly Considers The References Collectively Before Establishing A Basis For The Combination

Applicant submits that prior references cannot be considered collectively until the Examiner points to some motivation to combine those references. The purpose behind this requirement is to prevent the Examiner from using the invention itself and hindsight reconstruction to defeat the patentability of the invention. The Federal Circuit, in a recent

decision, articulates this position:

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

See In re Rouffet et al., 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). It is readily apparent that the law of *In re Rouffet* requires the Examiner to present soundly reasoned arguments based upon the substance of the cited references.[1] Moreover, the law does not regard the Examiner as one skilled in the art. *See In re Rijckaert*, 28 USPQ2d 1955 at 1956 (Fed. Cir. 1993)("[T]he examiner's assumptions do not constitute the disclosure of the prior art."); *See id.* at 1957 ("[W]hen the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears."). Indeed, the Federal Circuit has made it clear that "[b]road, conclusory statements regarding the teachings of multiple references, standing alone, are not 'evidence.'" *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614 (Fed. Cir. 1999).

Applicants submit that the Examiner has not provided a sound explanation for combining these references as required by the law in *In re Rouffet*. What the Examiner has provided are unsupported and conclusory legal statements as to why the claimed invention is allegedly obvious over the combination of references. Therefore, Applicants submit that the Examiner's argument fails because the references do not suggest the desirability of making this combination.

Neither reference cited by the Examiner suggests a therapeutic composition comprising the antibodies as combined in the present invention, a fact the Examiner admitted in the previous Office Action.[2] Thus, in light of the holding of the Federal Circuit in *Dembiczak*, the Examiner's conclusory arguments of law are clearly ***not evidence*** of obviousness.

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[1] *Accord Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (stating that the examiner must present convincing line of reasoning supporting rejection).

[2] "***Neither*** Starnes *et al.*, nor Doherty *et al.*, disclose a composition comprising polyclonal antibodies directed against TNF-α, IL-6 and IFN-γ and ***a method of treatment*** with such composition." July 2, 1999, Office Action, pg 4. Emphasis added.

The Examiner provides the conclusory statement that "combining antibodies against all three cytokines in one pharmaceutical composition would have been obvious to one of ordinary skill in the art." However, the record is devoid of a citation to any basis for suggesting the desirability of combining these reference. The Examiner has not shown reasons why a skilled artisan would make the combination; the Examiner has merely stated what the Examiner believes. Such unsupported statements are exactly what the *Rouffet* court sought to prevent. The Federal Circuit stated:

> The Board did not . . . explain what specific understanding or technological principal within the knowledge of one of ordinary skill in the art would have suggested the combination. *Instead, the Board merely invoked the high level of skill in the art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technological advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection.* To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

In re Rouffet, 47 USPQ2d at 1458. Emphasis added.

As stated above, the Examiner has not "shown reasons" why there is a motivation to combine. Simply reciting a list of elements and then stating that it *prima facie* obvious to modify one reference to provide the invention does not satisfy the legal standard.

2. The Examiner's Reliance On *In re Kerkhoven* Is Misplaced

Applicant notes the Examiner's reliance on the case of *In re Kerkhoven*. While the Examiner did not provide a citation, Applicants assume that the Examiner is citing to the case of *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069 (CCPA 1980). Applicant submits that reliance on the holding of *In re Kerkhoven* is misplaced for a number for reasons.

A. *In re Kerkhoven* Has Been Discredited In The Federal Circuit

The Federal Circuit's only two decisions discussing *In re Kerkhoven*, 626 F.2d 846 (C.C.P.A. 1980) are both **unpublished** and thus under the Federal Circuit's own rule 47.6(b) "shall not be employed or cited as precedent." Federal Circuit Local Rule 47.6(b). *In re Cooray*, 965 F.2d 1063 (Fed. Cir. 1992), the most recent Federal Circuit case to discuss *Kerkhoven*, the court severely discredits *Kerkhoven's* rational. The Federal Circuit stated in the

In re Cooray that it was not persuaded by the Board's citation to the concededly erroneous rational of *In re Kerkhoven. See Cooray,* 965 F.2d 1063. In fact, in *Cooray* the Board itself abandoned the *Kerkhoven* rational:

"On appeal the Solicitor concedes the Board's finding . . . is in error. He also contends that on Reconsideration, the Board abandoned its earlier *Kerkhoven* rational." It is thus apparent that the *In re Kerkhoven* rational holds no sway with the Federal Circuit and (apparently) the Board. Thus, the Examiner's reliance on the holding of *In re Kerkhoven* is improper on this ground alone.

B. *In re Kerkhoven* Is Distinguishable From The Present Case

In *Kerkhoven* the court faced a situation factually distinct from that presented here. In brief, the applicant in *Kerkhoven* appealed the rejection of **method** claims drawn to mixtures of anionic and nonionic detergents. The Court distinguished *Kerkhoven's* two claimed **methods** for producing detergent compositions: 1) methods in which the slurries (*i.e*, an anionic detergent ingredient slurry and a nonanionic detergent ingredient slurry) are independently dried and then mixed; and 2) methods in which the slurries (*i.e*, an anionic detergent ingredient slurry and a nonanionic detergent ingredient slurry) are simultaneously dried and mixed.[3] The *Kerkhoven* court determined that the claims on appeal encompassed one or both of two categories (*i.e.*, some of the claims encompassed both methods, while, claim 5 encompassed method 2 only).

The court agreed with *Kerkhoven* that Claim 5 was unduly lumped together with the other claims and that it was **not** obvious under the prior art because the prior art did not teach or suggest *Kerkhoven's* particular methods of producing detergent compositions. *See id.* Most importantly, the applicant in *In re Kerkhoven* **admitted** that the prior art taught the desirability of combining anionic and nonanionic detergent ingredients "[a]ppellant explains in his specification that the detergent-making art often prefers such [combinations of anionic and nonanionic detergent ingredients] detergents to achieve optimal detergent properties."

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[3] Each of these claim sets encompassed the common step of forming at least one slurry of the detergent ingredients, the active detergent content of one slurry being primarily if not exclusively anionic in nature and the active detergent content of the other slurry being primarily if not exclusively nonionic in nature.

Kerkhoven, 626 F.2d 846.[4] Applicant have made no such admissions about the prior art. Indeed, Applicants provided a reference (in a previous Response) to the Examiner which stated the undesirability of compositions of anticytokine antibodies.

C. Even if *In re Kerkhoven* Is Improperly Followed, The Examiner's *Prima Facie* Case Of Obviousness Is Rebuttable

The *In re Kerkhoven* court in holding that certain claims were obvious under the prior art stated "[i]t is **prima facie** obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose." *Kerkhoven*, 626 F.2d at 850. Emphasis added. The Manual Of Patent Examining Procedure, specifically at Section 2142, discusses the *prima facie* case of obviousness as a procedural for assigning the burden to go forward with presenting evidence of obviousness or nonobviousness as the case may be. Under the rules of patent procedure, a *prima facie* case is rebuttable and the Examiner **must** consider Applicants evidence of nonobviousness.

While Applicants DO NOT concede that the Examiner has established *prima facie* obviousness - even if (for argument's sake) the Examiner could rely on the *In re Kerkhoven* rationale, it only gives the Examiner a rebuttable argument. The Examiner must consider Applicants' failure data, presented in an earlier response, and their citation to a paper in the prior art discussing the undesirability of combined anticytokine therapies.

4. Even if References are Combined They do not Provide a Reasonable Expectation of Success

In order to establish a *prima facie* case of obviousness the prior art must, when combined, lead to a reasonable expectation of successfully producing the invention. MPEP § 2143.02. Applicant respectfully submits that one of ordinary skill in the art would not reasonably expect to produce the claimed invention by combining the cited references.

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[4] The court did determined that the broader claims were obvious and it is only in this context that the following statement was made: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose." *Kerkhoven*, 626 F.2d at 850.

A. Applicant Submitted Failure Data Demonstrating Nonobviousness

Applicant again directs the Examiner's attention to the failure data in the Specification. Applicant points to Table 3 in the Specification where: 1) anti-IFN-γ antibodies administered alone (60 minutes post challenge) failed to save any test animals; and 2) the combination of anti-TNF ***and*** anti-IFN-γ antibodies (administered 60 minutes post challenge) failed to save any test animals.

Contrary to Applicants' results in Table 3, shown above, Doherty *et al.* showed decreased morbidity in test animals upon administration of anti-IFN-γ antibodies ***alone***. Thus, Doherty *et al.* actually suggests the singular administration of anti-IFN-g antibodies and not the co-administration of anti-IFN-γ antibodies with other anti-cytokine antibodies as disclosed by the present invention. Moreover, contrary to Applicant's results, the Examiner cited both Starnes *et al.* and Doherty *et al.* as teaching administration of anti-TNF-a antibodies ***alone*** decreases morbidity in test animals. The Examiner implicitly argued that because these references ***individually*** teach decreased morbidity in respective test animals, that when they are combined they must also decrease morbidity in test animals because "one therapeutic composition would be expected to give synergistic and more robust effect against septic shock, it would have been easier to administer one composition to a patient than it is to administer three different compositions." July 2, 1999, Office Action, page 5. However, Applicant reminds the Examiner, that the law holds that the Examiner is not skilled in the art, nor, are the Examiner's conclusory assertions evidence of unpatentability. Thus, the Examiner's assertion as to the presumptive ***clinical benefits*** of co-administering anti-TNF ***and*** anti-IFN-γ antibodies to "give synergistic and more robust effect" is without the support required by the law of *In re Rouffet* and is contrary to the Applicant's empirical data. Indeed, the Applicant empirically showed that the co-administration of anti-TNF ***and*** anti-IFN-γ antibodies failed to save any test animals in the test system. The Applicant achieved an unexpected result however and overcame the morbidity associated with the co-administration of anti-TNF ***and*** anti-IFN-γ antibodies by administering the combination of anti-TNF antibodies, anti-IFN-γ antibodies and anti-IL-6 antibodies, as shown in Table 5.

Applicant submits that the failure data in the instant Specification underscores the non-obviousness of the present invention. The Examiner's rejection is thus unwarranted.

B. Obvious To Experiment is Not The Standard For Examination

The Federal Circuit has held that "obvious to experiment" is not the standard for obviousness. *See In re Dow Chemical*, 5 USPQ 2d 1529, 1532 (Fed. Cir. 1988). The Federal Circuit made it very clear that one must determine whether "the prior art would have suggested to one ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art." *Dow* at 1531. Emphasis added.

Applicant again submits that the Examiner examined the present invention under an impermissible "obvious to experiment" standard. The prior art does not suggest a reasonable chance of success for compositions combing the relevant anti-cytokine antibodies nor does the prior art suggest a reasonably successful therapeutic method for the use of such composition.

In regards to the Examiner rebuttal of the Opal *et al.* report, the Examiner cannot pick and chose among the elements of a reference on an *ad hoc* basis where it benefits the rejection. Opal *et al.* were encouraged by reports of others involving combinations of inhibitors. Opal *et al.*, page 1415, right hand column. However, when actual experiments were performed, Opal *et al.* concluded that "[c]ombination anticytokine therapy may exacerbate systemic infection and worsen [the] outcome in experimental sepsis." Opal *et al.*, Abstract, lines 11-12. The Examiner agrees with the Applicant by admitting that "[the] Opal *et al.* reference teaches against simultaneous inhibition of certain cytokines." Office Action, page 5.

Thus, the Examiner's assertion that one skilled in the art would be motivated by an expectation of successfully combining the references (Doherty *et al.* and Starnes *et al.*) is decisively undermined by the fact that the Examiner has admittedly failed to cited a reference teaching the combined administration of these anti-cytokine antibodies, particularly, in the face of the Applicant bringing to the Examiner's attention a reference directly in opposition to the Examiner's assertion--a point which the Examiner expressly admits.

Moreover, the Examiner also admits to the "***dichotomous*** roles of... [cytokines] in the host response to invasive bacterial infection." Office Action, page 5. Emphasis added. It appears that the Examiner has implicitly argued that simultaneous administration of two or more anticytokine antibodies must be empirically determined. Applicant submits that empirical results are beyond prediction even for one skilled in the art, and are thus by

definition nonobvious. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness and this rejection should be withdrawn.

C. The Combined References Do Not Teach Every Claim Limitation

Under MPEP § 2143.03 to establish a *prima facie* case of obviousness the combined art references must teach all claim limitations. Applicant resubmits that the combination of Starnes *et al.* and Doherty *et al.* does not teach all the limitations found in the Claims. In particular, Applicant submits that neither reference teach the combination of two anti-cytokine antibodies (let alone the combination of anti-TNF and anti-IL-6 antibodies). The Examiner has not produced a single contradictory reference.

As stated previously, the Examiner admits that Starnes *et al.* does "not disclose a composition comprising both antibodies to TNF-α and IL-6 or a method of treatment with such composition." Office Action, page 3. Moreover, the Examiner admits that Doherty *et al.* teach compositions "with ***either*** anti-IFN-γ polyclonal antibodies ***or*** anti-TNF-α polyclonal antibodies." Office Action, page 3-4. Emphasis added. It is thus apparent that the Examiner admits that even when the references are combined they still do not "disclose a composition comprising polyclonal antibodies directed against TNF-α, IL-6, and IFN-γ." Office Action, page 4. By the Examiner's own admissions, neither reference teaches a composition wherein more than one type of anti-cytokine antibody are co-administered.

Furthermore, Doherty and Starnes only perform protection type experiments. That is to say, antibody is given first, followed by a chalenge with LPS or *E. coli.* The Examiner is asked to note that original Claim 13 specifies that treatment must be after symptoms of sepsis. This claim is supported by the rescue type of experiments set forth in the specification. As such, the Examiner has cited art that fails to teach all the limitations of the claimed invention. Consequently, a *prima facie* case of obviousness has not been established and this rejection should be withdrawn.

6. The Emery Reference Does Not Remedy The Other Art

The Examiner reasserts the rejection of Claims 1, 3-6 and 16-18 as allegedly obvious over the combination of Starnes *et al.*, and Doherty *et al.*, in view of Emery *et al.* Office Action, page 5. The Examiner states that "[t]he rejection is maintained for the reasons set forth in pages 5-6 in Paper No. 4 (July 2, 1999)." Applicant respectfully traverses this rejection. The addition of Emery to the combination of references does not remedy the above-discussed deficiencies of Starnes and Doherty. Emery teaches nothing about sepsis and cytokines.

CONCLUSION

For the reasons set forth above, Applicant respectfully submits that all pending claims are currently in condition for allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (617) 252-3353.

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